PATENT SPECIFICATION

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COMPLETE SPECIFICATION

NO DRAWINGS

Pharmaceutical Compositions Containing Phloroglucinol

We, ORSYMONDE, of 166 rue de Charonne, Paris XI, France, a French body corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

Phloroglucinol (1,3,5-trihydroxy-benzene) is a solid in the form of rhombohedric prisms, the crystals of which include two molecules of water of crystallisation. The hydrated material melts at 117°C. and, if anhydrous, it melts around 218°C. under rapid heating and between 200° and 209°C. under gentle heating; this substance is soluble in water and slightly soluble in alcohol and ether.

It has been discovered that phloroglucinol has very interesting antispasmodic properties. Numerous pharmacological tests have been carried out in order to verify that phloroglucinol can be used safely and with a high activity in therapeutics.

In the first place, acute toxity tests have been carried out. Acute toxicity has been determined intra-peritoneally on white mice. 44 female mice of the Webster strain having a weight between 16 and 25 g. have been tested. Toxicity has been studied for dosages from 0.25 to 2 g. per kg.; even at this latter dosage, no immediate mortality has been observed. However, two mice out of twelve died after 23 hours.

Even at this dosage of 2 g. per kg., no respiratory, cardiac or convulsive toxic phenomenon was noted after the injection. Merely a certain transient stimulation of the animal with running movements was observed.

In all cases, an abdomenal contraction syndrome with elongation of the hindquarters was noted, which phenomenon persisted for 5 to 10 mins.

Intravenous toxicity tests have also been carried out on dogs anaesthetised with chloral, by injecting doses varying from 25 to 250 mg. per kg.: even at this latter dosage, which was injected into 8 dogs, no mortality was observed.

Study of the chronic toxicity of phloroglucinol has shown that, in doses markedly greater than active doses, the administration of this compound is entirely without any risk; the growth of rats absorbing phloroglucinol mixed in concentrations of 0.15-0.62% with their food was not reduced in comparison with control rats. Hematological examination disclosed no anomalies. Examination of the vital organs and the weights of these organs showed no detectable difference in comparison with the controls; in particular, there was no antithyroid action at these doses.

Females were mated with males; the fertility and fecundity of animals to which phloroglucinol was administered were not substantially different from those of control animals.

First generation animals had absorbed the product during the 200 days and those of the second generation during 60 days; no toxic or subtoxic phenomena were observed.

The antispasmodic effect of phloroglucinol was then studied. For this, in a first series of experiments, female rats having a weight ranging between 75 and 200 g. were used, which were previously unfed for 20 hours. The duodena of these rats were taken and maintained alive in a standard Tyrode solution prepared with double distilled water oxygenated by aeration, the organs being maintained at a constant temperature of +32°C.

29 rats were used in these experiments and each test was made on two organs of these animals.

Phloroglucnol was used in 1% aqueous so-

[Price 4s. 6d.]

lution and in 5% saturated solution and added to Tyrode liquid so as to have a total volume of 80 ccs. in each test tube.

For the dosage, the peristaltic movements were recorded when, after 15 to 20 minutes immersion in the Tyrode solution, the duodenum was relaxed and about 10 mg. of barium chloride had been introduced into the bath. The preparation was washed, immediately after observing a muscle contraction and a state of persistent spasm, by means of a Tyrode solution. After 15 mins., the experiment was repeated; if an identical response was obtained, the preparation was washed immediately. The same quantity of barium chloride was then added to the Tyrode liquid containing the duodenum and, without effecting washing, 0.05 g., 0.10 g. and 0.15 g. of phloroglucinol per 80 ccs. was added.

In each case, an antispasmodic effect was obtained which, was the greater as the dose of phloroglucinol was larger. The effect increased with the concentration.

On average, the dose of 50 mg. for 80 ccs. of Tyrode exerted an antispasmodic action of 42%, the 100 mg. dose an action of 70% and the 150 mg. dose an action of 81%.

It was thus shown that phloroglucinol exerts a preventive effect on the spasmogenic action of barium chloride on isolated rat duodena.

Phloroglucinol has the property of alleviating the spasm of muscular origin, produced by barium chloride on the duodenum of the rat. The effect of phloroglucinol is reversible by washing, also. After producing a moderate spasm by means of barium chloride and then alleviating the spasm with phloroglucinol, the muscle can be restored to its initial condition, by repeated washing and prolonged rest.

The antispasmodic effect of phloroglucinol has also been studied on the duodenum and ileum of the dog *in situ*. This action was studied on the intestinal spasm produced by barium chloride in dogs subjected to artificial respiration; the experiment was made on dogs anaesthetised with chloralose.

In all cases, 200 mg. of phloroglucinol per kg., injected intravenously, were sufficient to alleviate the spasm produced by 3 mg. of barium chloride per kg. Slowing of the peristaltic contractions was also observed.

Study of the antispasmodic action of phloroglucinol has also been made on isolated dog and guinea-pig ureters. It has been established that, on these isolated organs, phloroglucinol does not modify the effect of acetylcholine, although it is alleviated by atropine; phloroglucinol alleviates the spasm produced by barium chloride and is capable of preventing the spasmogenic effect of barium chloride on the isolated ureter.

This product thus exerts on the isolated ureter an effect analogous to that observed on a smooth muscle such as an isolated rat duodenum.

An attempt was also made to establish the pharmaco-dynamic spectrum of phloroglucinol.

The cardio-vascular effect was studied upon dogs normotensively anaesthetised with chloral.

The carotid pressure of several dogs was recorded and it was observed that injection of 25 to 75 mg. per kg. of phloroglucinol caused no change in this pressure.

On the contrary, with all the animals, injection of 200 to 250 mg. per kg. of phloroglucinol caused a diminution in the carotid pressure which varied according to the animals from 20 to 60%.

The coronary vasodilator effect was studied by the classical technique of Langendorff, on isolated rabbit heart. For this purpose, an isolated rabbit heart was suffused using an oxygenated Van Dyke Hastings solution. After having established the output of suffusion of the base, a dilute solution of phloroglucinol was injected into the tube connecting the suffusing device to the nozzle. This experiment was carried out on several rabbits; doses from 0.1 to 10 mg. of phloroglucinol were without effect. Doses of 50 to 100 mg. of phloroglucinol caused vasodilation, ranging between 10 and 200%.

Clinical tests have also been carried out, at the Hôpital Bichat in Paris, patients being given cachets containing phloroglucinol in different doses and cachets solely containing glucose.

With twenty patients, it was observed that phloroglucinol, employed in the form of cachets containing one part by weight of phloroglucinol to nine parts by weight of glucose, had a certain efficacy as an antispasmodic and were tolerated perfectly.

On another twenty patients suffering from hepatitis, phloroglucinol inhibited, in almost every case, the depression caused by the influence of sodium chlorate and morphine.

1 to 3 cachets per day containing 10 mg. of phloroglucinol and 90 mg. of glucose, in the case of calcified cholecystitis and hepatitis, diminished and often even eliminated the depression.

On the other hand, twelve patients had their nephritic crises calmed by the administration, during the period of depression, of two cachets each containing 5 mg. of phloroglucinol.

It was observed that phloroglucinol exerted a certain effect in each case, even in a dose of 1/10 mg., use in the form of cachets, capsules, powders or tablets giving equally good results.

Other clinical tests carried out at the Hôpital Saint Louis in Paris have shown that phloroglucinol has a spectacular action

in the treatment of nephritic colic, the product being associated with a reducing sugar such as glucose, fructose or levulose in doses of 5 to 40 mg. per dosage unit (cachet or tablet).

The present invention accordingly consists in a pharmaceutical composition in unit dosage form as hereinafter defined for administration orally or by injection, useful as an antispasmodic, which comprises phloroglucinol and one or more diluents or carriers admixed therewith. The other substance or substances may be a solid or liquid carrier or a dispersant for the phloroglucinol and the composition may be made in the form of a cachet, tablet, powder, capsule or injectable ampoule.

"A pharmaceutical composition in unit dosage form" is intended to refer to a physically discrete unit containing an individual quantity of the active material (i.e. phloroglucinol) in association with a pharmaceutical diluent or carrier, the quantity of active material being such that one or more units are required for a single therapeutic administration. The term does not refer to mere solutions in water or other common solvents except when such are packed in ingestable containers or have been prepared so as to be acceptable for parenteral injection.

The following six illustrative examples of compositions according to the invention are provided.

Example	*Nature of Dosage Unit*	*Components*	*Composition per Dosage Unit*
1	Cachet	phloroglucinol	0.04 g.
		glucose	0.30 g.
2	Cachet	phloroglucinol	0.08 g.
		lactose	0.22 g.
3	Capsule	phloroglucinol	0.05 g.
		glucose	0.15 g.
4	Sugared Tablet	a) *centre*	
		phloroglucinol	0.040 g.
		lactose	0.120 g.
		sucrose	0.020 g.
		starch	0.015 g.
		magnesium stearate	0.003 g.
		sodium lauryl sulphate	0.003 g.
		talc	0.003 g.
		b) *coating*	
		gelatine	traces
		white wax	traces
		talc	0.060 g.
		sucrose	as desired, up to 0.40 g.
		c) *colouring*	
		patent blue	as desired
5	Injectable Ampoule	phloroglucinol	0.01 g.
		glucose	0.04 g.
		bi-distilled water	as desired, up to 1 ml.
6	Injectable Ampoule	phloroglucinol	0.005 g.
		glucose	0.045 g.
		bi-distilled water	as desired, up to 1 ml.

WHAT WE CLAIM IS:

1. A pharmaceutical composition in unit dosage form as hereinbefore defined for administration orally or by injection; useful as an antispasmodic, which comprises phloroglucinol and one or more diluents or carriers admixed therewith.

2. A pharmaceutical composition as claimed in claim 1, which also contains a reducing sugar.

3. A pharmaceutical composition as claimed in claim 2, in which the sugar is glucose, fructose or levulose.

4. A pharmaceutical composition as claimed in claim 3, which comprises 1 part by weight of phloroglucinol and 9 parts by weight of glucose.

5. A pharmaceutical composition as

claimed in any preceding claim, which is in the form of a cachet, tablet, powder, capsule, or an ampoule containing an injectable composition.

6. A pharmaceutical composition as claimed in claim 5, in which the dosage unit contains 5 to 40 m.g. of phloroglucinol.

7. A pharmaceutical composition as claimed in any preceding claim, which contains a solid or liquid or dispersant carrier for the phloroglucinol.

8. A pharmaceutical composition in unit dosage form according to claim 1, substantially as hereinbefore described.

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PROVISIONAL SPECIFICATION

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The Applicant has discovered that phloroglucinol has very interesting antispasmodic properties.

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In the first place, acute toxicity tests have been carried out. Acute toxicity has been determined intra-peritoneally on white mice. 44 female mice of the Webster strain have been tested, having a weight between 16 and 25 g. Toxicity has been studied for dosages from 0.25 to 2 g. per kg.; even at this latter dosage, no immediate mortality has been observed. However, two mice out of twelve died after 23 hours.

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It was observed that phlorogucinol exerted a certain effect in each case, even in a dose of 1/10 mg., use in the form of cachets, capsules, powders or tablets giving equally good results.

The present invention accordingly consists in a pharmaceutical composition suitable for use as an anti-spasmodic, which comprises phloroglucinol and one or more inert or active substances in admixture therewith. The other substance or substances may be solid or liquid, such as a solvent, dispersant or carrier for the phloroglucinol and the composition may be made in the form of a cachet, capsule or other dosed amount as described above.

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